Medicine
Health Physics
Industrial Hygiene
Toxicology
Medical Department/3M

3M Center
St. Paul, Minnesota 55101
612/733 1110

AR226-1376
Personal and Confidential

March 27, 1981

Blaine C. McKusick, Ph.D.
Haskell Laboratory
Elkton Road
Newark, Delaware 19711

Dear Blaine:

A copy of the TSCA Section 8(e) notification regarding perfluoroalkane carboxylic acids and corresponding ammonium carboxylates is enclosed. Please contact us if you have further questions.

Sincerely,

Frank

F. D. Griffith, Ph.D.
Manager, Toxicology Services

FDG:klh

Enclosure

AJP002950

EID079613

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Frank A. Ubel, M. D.
Medical Director

March 20, 1981

3M

Acting Director, NIOSH
Park Lawn Building
5600 Fishers Lane
Rockville, MD 20855

Dear Sir:

Subject: Notice to EPA Regarding Section 8(e)
of the Toxic Substances Control Act

Please find enclosed for your information a copy of the subject notice submitted to EPA on this date. You will note from our letter to EPA that we regard certain parts of this notice as trade secret or confidential business information. Therefore, this information should be handled according to Section 15 of the Occupational Safety and Health Act (29 USC 664). In the event you determine that it may be necessary to disclose certain of this information to the general public, we request that you contact 3M prior to such disclosure.

Very truly yours,

Frank A. Ubel, M.D.

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Enclosure

General Offices/3M
220 2E 3M Center
Saint Paul, Minnesota 55101
612/733 5181

Chemicals Division
3M Center
St. Paul, Minnesota 55144
612/733 1110

CERTIFIED M[illegible] - RETURN RECEIPT REQUESTED

March 20, 1981

Document Control Officer
Chemical Information Division
Office of Toxid Substances (WH-557)
Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Gentlemen:

Subject: Section 8(e) Toxic Substances Control Act (TSCA)
Perfluoroalkane Carboxylic Acids and Corresponding
Ammonium Carboxylates

Please find attached 3M Report entitled "Oral Rangefinder Study of T-2998CoC in Pregnant Rats", dated March 12, 1981. Preliminary information from this study has indicated that oral dosing of the subject ammonium carboxylate mixture produces the described teratogenic effects. This Report and the findings described in the article published in the August 1980 American Industrial Hygiene Journal and referenced as part of 8EHQ-1180-0374C, forced us to submit this information pursuant to Section 8(e) of TSCA and EPA's statement of interpretation published in the FEDERAL REGISTER, March 16, 1978.

Perfluoroalkane ammonium carboxylates is a generic chemical name for a mixture of homologs which can be expressed by the general formula $C_nF_{2n+1}COO^-NH_4^+$. Each of these homologs was reported on the TSCA Inventory

As previously stated in our November 19 submission, our employee records and epidemiology data indicate that to date no human health problems have been observed nor disease patterns detected which are attributable or related to fluorochemical exposure. This mixture of homologous ammonium carboxylates and the corresponding homologous carboxylic acids are currently commercially available and used as follows:

3M Brand Fluorochemical Acid FC-26	Emulsifier additive in chemical specialty products (international market only)

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FLUORAD® Brand Fluorochemical Surfactant FC-126 (ammonium carboxylates)	Additive used in chemical specialty products
FLUORAD® Brand Fluorochemical Surfactant FC-143 (ammonium carboxylates)	Emulsifier used in chemical processing and as an additive in chemical specialty products

At our Chemolite production facility, located at Highway 61 and Washington County Road 19, St. Paul, MN 55133, the subject chemicals are manufactured from of locally-produced perfluoroalkane carboxylic acids and of the same acid imported from our European plant in Antwerp, Belgium. Chemical reaction occurs in a closed system. Approximately 36 employees are intermittently exposed to the subject chemicals during production at the Chemolite facility. Approximately of perfluoroalkane carboxylates are exported annually.

We plan to inform, by April 1, those customers and 3M employees who have, through uses and/or processing, potential significant exposure to the subject chemicals. At that time, we will summarize these findings and outline our recommendations for handling and using these products. We are by copy of this letter advising NIOSH of these new preliminary teratogenic findings. As additional information becomes available to us, we plan to advise these customers and employees accordingly.

In view of the attached preliminary findings and in line with our ongoing testing and monitoring program on fluorochemicals, the following program is planned for the ammonium carboxylate mixture:

(1) A teratogenicity study in rats.

(2) A subsequent teratogenicity study in rabbits.

(3) Continual industrial hygiene program to improve and refine manufacturing and packaging processes which have been developed to further reduce the exposure to plant employees.

Since certain of the information provided herein is considered confidential business information, we are providing a sanitized version of this report for the public file. In addition, we have deleted from the confidential submission inconsequential information such as the names of 3M employees for the purpose of protecting their privacy.

AJP002953

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Should additional correspondence be necessary on this matter, please contact:

Larry Magill
Manager, Regulatory Affairs Department
Commercial Chemicals Division
3M
3M Center, 223-6S-04
Saint Paul, MN 55144
Telephone: 612/733-7062

Yours very truly,

George L. Hegg
Group Vice President
Chemicals, Film & Allied Products

GLH:sue

Attachments

cc: Acting Director, NIOSH
Park Lawn Building
5600 Fishers Lane
Rockville, MD 20855

bc: R. J. Davis/T. J. Scheuerman - 220-12E
W. G. Ewert - 220-12W
F. D. Griffith/W. C. McCormick - 220-2E
C. W. Hanson - 223-6
G. L. Hegg - 220-13C
L. C. Krogh - 223-6
J. D. LaZerte/R. A. Prokop - 236-1
L. F. Ludford - 225-5N
W. H. Pearlson - 223-6
D. R. Ricker - 53-4
P. F. Riehle - Chemolite
W. F. Scown - 223-6
S. D. Sorenson - 220-2
F. A. Ubel/D. E. Roach

AJP002954

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Report Number: M-601

Date: March 12, 198

Oral Rangefinder Study of T-2998CoC in Pregnant Rats

Experiment No.: 0680RR0018

Conducted At: St. Paul, Minnesota

Dosing Period: January 20, 1980 to January 29, 198

Study Director:

2/24/81
Date

2/24/81
Date

2/25/81
Date

AJP002955

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Introduction

This oral rangefinder study[a] was conducted to determine the upper dose level of T-2998CoC[b] for a subsequent oral teratology study in rats. The study was sponsored by 3M Commercial Chemical Division, St. Paul, Minnnesota and was conducted by the Safety Evaluation Laboratory, St. Paul, Minnesota. The study was conducted in accordance with the Safety Evaluation Laboratory's Standard Operating Procedures for such studies. The storage location for the raw data and a copy of the final report is maintained in the Safety Evaluation Laboratory's record archives.

Methods

Thirty-six time-mated Sprague-Dawley derived female rats from Charles River Breeding Laboratory were used in the study. The animals were indiscriminately removed from the shipping boxes by Animal Care personnel and placed in the rack of cages from the left to right starting at the top and working down. Later the Study Director assigned dose groups by vertical rows. The rats were housed individually in hanging stainless steel cages with wire mesh floors and fronts in a temperature and humidity controlled room. Purina Laboratory Chow and water were available ad libitum. The lights were on a 12 hour light/dark cycle.

The animals were observed daily from day 3 through day 20 of gestation for abnormal clinical signs. Body weights were recorded on days 3, 6, 9, 12, 15 and 20 of gestation and the rats dosed accordingly using a constant dose volume of 5 ml/kg of body weight. T-2998CoC was suspended in corn oil and administered daily by oral intubation at doses of 150, 100, 75, 50 or 25 mg/kg/day to groups of 6 rats on days 6 through 15 of gestation. A control group of 6 rats received only corn oil by oral intubation on the same days. On day 20 of gestation the rats were killed by cervical dislocation and each uterus, including its contents, was examined immediately to determine if the animal was pregnant. Because two previous teratology studies (Experiment Nos: 0680TR0008 and 0680TR0010) with chemically related compounds resulted in fetuses with teratogenic changes in the lens of the eye, a few fetuses were also taken at day 20 of gestation and examined for eye abnormalities.

Blood samples from three rats in each dose group were taken before the first dose and at day 20 of gestation. Liver specimens were also taken from the same rats on day 20 of gestation. The plasma samples and liver specimens were frozen and submitted to the sponsor.

Results and Discussion

The oral administration of T-2998CoC at 150, 100, 75, 50 or 25 mg/kg/day to rats during the period of organogenesis (days 6 through 15 of gestation) did not result in any deaths. A toxic effect of reduced body weight gain occurred between days 6 and 9 of gestation in the 150 mg/kg/day dose group (Table 1).

The two nonpregnant 150 mg/kg/day rats had a more severe effect on body

[a] Experiment No. 0680RR0018
[b] FC-143

weight on day 9 of the study than the pregnant high dose dams (Appendix I). They lost a considerable amount of weight and one was observed to have urinary incontinence on days 11, 12 and 13. The pregnant dams of the 100, 75, 50 and 25 mg/kg/day dose groups did not have abnormal clinical signs and gained weight at comparable levels to the 0 mg/kg/day group.

Four fetuses were examined from each of four dams in the 150 and 25 mg/kg/day dose groups for eye changes. All of the readable fetuses sectioned had eye changes consisting of one or more of the following: large lens clefts, dark streak running one-half to three-quarters of the way through the lens or disorganized lens fibers (Table 2). The lens abnormalities occurred in the same location as those observed in the two previous teratology studies (Experiment Nos: 0680TR0008 and 0680TR0010) on chemically related compounds. The abnormalities in this study appeared more pronounced than in the previous studies. In the previous studies, the teratogenic effect was a developmental eye abnormality which appeared to be an arrest in development of the primary lens fibers forming the embryonal lens nucleus, followed by secondary aberrations of the secondary lens fiber of the fetal nucleus. The same general morphological changes occurred in this rangefinder study with T-2998CoC.

Conclusion

The objective of determining an upper dose level for an oral rat teratology study was met in this study. The above results suggest that the 150 mg/kg/day dose level would be an appropriate high dose in a rat teratology study because of the toxic effect of reduced body weight gain. In addition to the toxic effect of reduced body weight gain, the teratogenic effect of lens abnormality was observed and is likely to be reproduced in a teratology study.

Table 1

Oral Rangefinder Study of T-2998CoC in Pregnant Rats
Mean Body Weight Gains of Pregnant Rats
With Standard Deviations (g)

	Day				
	6	9	12	15	20
Control	36 4.2	18 7.4	21 7.5	29 1.6	76 10.7
150 mg/kg/day	21 5.5	5 17.8	36 a 8.8	12 13.8	84 12.1
100 mg/kg/day	29 4.1	15 5.1	17 4.4	19 12.6	84 13.5
75 mg/kg/day	27 6.6	11 10.6	21 2.7	19 10.5	74 12.6
50 mg/kg/day	30 6.5	16 3.7	23 5.6	27 7.3	76 10.6
25 mg/kg/day	24 3.6	16 6.4	24 6.9	29 9.3	82 5.8

a Significantly higher than the control (Dunnett's t test $p < 0.05$)

Table 2

Oral Rangefinder Study of T-2998CoC in Preqnant Rats
Ratios of Fetuses with Eye Changes to Fetuses Examined[a]

High Dose Group (150 mg/kg/day)	Low Dose Group (25 mg/kg/day)
16/16	15/15[b]

[a] Four fetuses examined from each of four dams
[b] One fetus not examined because eye architecture destroyed in sectioning

Appendix I

Oral Rangefinder Study of T-2998CoC in Pregnant Rats

Individual Body Weights (g) and Mean Body Weights with Standard Deviation for Pregnant Rats

		Day					
		3	6	9	12	15	20
0 MG/KG/DAY							
N1R	316	194	223	244	269	297	382
N1R	317	186	214	238	262	292	376
N1R	318	192	217	227	253	282	365
N1R	319	207	239	250	258	285	360
N1R	346	190	231	257	280	311	369
MEAN		190	225	243	264	292	369
STAN. DEV		7.7	10.3	11.5	10.5	11.5	8.2
NON PREGNANT ANIMALS							
N1R	320	184	212	224	215	222	222

		Day					
		3	6	9	12	15	20
150 MG/KG/DAY							
O1R	321	202	222	216	257	287	367
O1R	324	192	218	217	257	281	341
O1R	325	177	191	222	241	242	314
O1R	347	206	232	226	262	278	378
MEAN		195	216	220	255	267	351
STAN. DEV		12.9	17.5	4.6	7.7	19.4	28.3
NON PREGNANT ANIMALS							
O1R	322	207	228	198	200	219	246
O1R	323	181	205	181	196	215	231

Appendix I (Continued)

Oral Rangefinder Study of T-2998CoC in Pregnant Rats

Individual Body Weights (g) and Mean Body Weights with Standard Deviation for Pregnant Rats

	Day					
	3	6	9	12	15	20
100 MG/KG/DAY						
P1R	326	184	193	210	229	253	327
P1R	327	214	240	248	268	285	331
P1R	328	262	286	302	317	349	452
P1R	329	200	235	245	256	268	353
P1R	330	185	218	234	248	268	363
P1R	348	189	218	240	263	296	371
MEAN		202	232	247	264	282	366
STAN. DEV		33.6	31.3	30.4	29.6	34.9	45.5

	Day					
	3	6	9	12	15	20
75 MG/KG/DAY						
Q1R	331	192	221	243	265	288	346
Q1R	332	198	212	228	249	271	346
Q1R	333	172	203	215	235	263	346
Q1R	334	211	242	236	261	270	326
Q1R	335	193	216	225	244	268	321
Q1R	349	206	231	248	265	293	382
MEAN		194	221	233	253	272	346
STAN. DEV		12.9	11.1	12.2	12.4	10.6	20.6

Appendix I (Concluded)

Oral Rangefinder Study of T-2998CoC in Pregnant Rats

Individual Body Weights (g) and Mean Body Weights with Standard Deviation for Pregnant Rats

		Day					
		3	6	9	12	15	20
50 MG/KG/DAY							
R1R	336	193	219	236	253	276	350
R1R	337	177	201	213	235	259	338
R1R	338	226	251	262	283	314	397
R1R	339	170	198	218	237	264	308
R1R	340	187	226	245	267	304	378
R1R	350	192	229	243	276	308	382
MEAN		191	221	236	259	286	359
STAN. DEV		19.4	19.6	18.2	20.1	26.2	33.0

		Day					
		3	6	9	12	15	20
25 MG/KG/DAY							
S1R	342	216	239	266	283	304	388
S1R	343	207	234	249	279	304	383
S1R	344	185	208	227	253	292	369
S1R	345	200	219	233	249	270	348
S1R	351	205	233	238	268	307	398
MEAN		203	227	243	266	295	377
STAN. DEV		11.4	12.8	15.4	15.2	15.3	19.4
NON PREGNANT ANIMALS							
S1R	341	187	203	219	220	228	238

DISTRIBUTION LIST

E. G. Gortner (original + 1)

E. G. Lamprecht

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W. C. McCormick → F. D. Griffith → F. A. Ubel (5)